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ARDS phenotypes and response to therapy: the dawn of personalised medicine for ARDS

Manu Shankar-Hari[1,2] and Daniel F. McAuley[3,4#]

Manu Shankar-Hari[1,2] M.Sc., Ph.D.

[1]Department of Critical Care Medicine, Guy's and St Thomas' NHS Foundation Trust, Westminster Bridge Rd, London SE17EH, United Kingdom; [2]Division of Asthma, Allergy and Lung Biology, King's College London, United Kingdom

email: manu.shankar-hari@kcl.ac.uk

[3]Centre for Experimental Medicine, Wellcome-Wolfson Institute for Experimental Medicine, Queen's University of Belfast, Belfast, Northern Ireland; [4]Regional Intensive Care Unit, Royal Victoria Hospital, Grosvenor Road, Belfast, Northern Ireland

email: d.f.mcauley@qub.ac.uk

[#]corresponding author

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Acute respiratory distress syndrome is a heterogeneous clinical condition characterised by complex pathophysiological mechanisms such as dysregulated pulmonary and systemic inflammation, diffuse alveolar epithelial and endothelial cell injury and altered alveolar membrane permeability (1, 2). ARDS remains common (3) with high mortality of 48% (45% - 51%) in observational studies and 37% (34% - 41%) in clinical trials (4). There are no pathognomonic signs or diagnostic tests for ARDS (5). For diagnosis at the bedside, the ARDS definition identifies clinical phenotypes with predictive validity categories based on the severity of hypoxaemia to supplement clinical judgement and radiological findings. However due to the underlying biological differences within the overall clinical phenotype, these categories do not necessarily equate to generic treatment responses and interventions may only be effective in a sub-population of the overall cohort of patients with ARDS in a randomised clinical trial (RCT) (1). Therefore whether it is possible to identify these ARDS treatment response groups is an important question.

ARDS phenotype subsets (subphenotypes) represent patient groups within a heterogeneous ARDS cohort with a similar set of observable clinical, radiological, biological and/or outcome characteristics. ARDS endo-phenotypes (endotypes) represent patient subsets of ARDS defined either by a biologically restricted molecular pathway/mechanisms or by differences in treatment response or rarely both. Our current understanding of *causal* determinants (6) of clinical, radiological and biological manifestations, treatment responses, outcomes and their inter relationships is incomplete. ARDS literature like the sepsis literature is replete with RCTs where there are no differences in the average treatment effect between the intervention and control arms. Identifying *ARDS subgroups* with either an improved average treatment effect or a decreased variation in treatment response or a greater event rate or combinations thereof, may make it possible to reduce the probability of trials that show no statistically significant difference in average treatment effect (7). Reanalysis of data from completed RCTs with an emphasis on identifying these subgroups within the ARDS phenotype-endotype continuum represents a novel approach.

Latent class analysis (LCA), highlighted Lazarsfeld by in the 1950s (8), is one approach to identify clustering within cohorts, by testing the hypothesis that two or more unobserved categories (latent classes) explain the relationships between observed variables

in the cohort. The primary goal of LCA is to identify the most parsimonious set of predictor variables and latent classes that explain the cohort data. LCA assumes that all data points have conditional independence and come from one of these unobserved categories. The granularity of data is reduced to standard normal distribution for analysis. The choice of variables, the model characteristics and the number of latent classes are dependent on the methods used (9-11). Therefore LCA could potentially identify these *ARDS subgroups*.

Using LCA of data from the ARMA and ALVEOLI RCTs in ARDS, Calfee and colleagues previously reported two ARDS subgroups with distinct clinical, biological and outcome characteristics with one subgroup characterised by a higher prevalence of shock, greater inflammation and endothelial injury and higher mortality (12). Significant interaction between the subphenotype and response to PEEP was also identified. In this issue, Famous K et al replicate these findings using data from the FACTT trial(13). They show that the two-class LCA model, with one group again characterized by hypotension, inflammation and mortality still holds true. Significant interaction between the subphenotypes and fluid regimen was also observed.

This important body of work represents the beginning of personalised medicine for ARDS by improving our understanding of disease mechanisms, treatment response characteristics, and outcome determinants. This work could allow researchers to delineate causal mechanistic pathways in the development of ARDS, which could help tailor treatment accounting for individual heterogeneity. The ability to identify patient cohorts who are more likely to respond to a specific therapy (predictive enrichment)(14) could represent a major advance in clinical trial design in ARDS. Several additional questions remain. First, data to support these *ARDS subgroups* are limited to the specific population recruited into ARDSnet RCTs. Thus it would be useful to replicate and validate these findings in ARDS population from other international RCTs and whether these *ARDS subgroups* could be identified within unselected observational cohorts. Second, it is important to know if a patient's *ARDS subgroup* allocation changes over time as this could have implications for the timing of interventions. Finally it is important to highlight that caution is required with *causal* and *treatment response* inferences as the premise of randomisation may no longer be valid in these analyses. This last point that is perhaps the most fundamental challenge, is best

addressed in clinical trials designed to specifically test the hypothesis that these ARDS endotypes can be identified prior to randomisation and are associated with an increased likelihood of a positive treatment response (statistically significant average treatment effect). Such trials will be enabled by the development of point of care assays for recognition of ARDS endotypes in real-time. In terms of the current work, these data also raise the potential the need to re-visit fluid therapy in ARDS patients.

What are the implications of this research going forward? The authors have shown unequivocally that there is an urgent need for further research to understand these *ARDS subgroups* within the complex phenotype-endotype continuum and to establish uniform reporting standards. Calfee and colleagues(12, 13) have done an excellent service to our speciality by highlighting a fresh approach to study patient heterogeneity, which is likely to both improve our understanding of the pathophysiology of ARDS as well as inform future trials in ARDS as a new era of personalised medicine for ARDS emerges.

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